Journal of
Clinical & Cellular Immunology

Drew et al., J Clin Cell Immunol 2016, 7:6
DOI: 10.4172/2155-9899.1000469

Short Communication Open Access

Peroxisome Proliferator-Activated Receptor-γ Agonists: Potential Therapeutics for Neuropathology Associated with Fetal Alcohol Spectrum Disorders

Paul D. Drew and Cynthia J.M. Kane*

Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, Little Rock, AR, USA

***Corresponding author:** Cynthia J. M. Kane, Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, Biomedical Research Center II, Room 560-2, 4301 W. Markham St., Slot 846, Little Rock, AR 72205, USA, Tel: 1-501-626-9995; Fax: 1-501-526-6756; E-mail: kanecynthiaj@uams.edu

Received date: October 06, 2016; **Accepted date:** November 09, 2016; **Published date:** November 14, 2016

Abstract

Fetal alcohol spectrum disorders (FASD) result from fetal exposure to alcohol during pregnancy. These disorders present a variety of sequelae including involvement of the central nervous system (CNS) with lasting impact on cognitive function and behavior. FASD occur at an alarming rate and have significant personal and societal impact. There are currently no effective treatments for FASD. Recent studies demonstrate that ethanol induces potent neuroinflammation in many regions of the developing brain. Furthermore, anti-inflammatory agents such as peroxisome proliferator-activated receptor (PPAR)-γ agonists suppress ethanol-induced neuroinflammation and neurodegeneration. This suggests that anti-inflammatory agents may be effective in treatment of FASD. Future studies designed to determine the specific mechanisms by which alcohol induces neuroinflammation in the developing CNS may lead to targeted therapies for FASD.

Keywords: Brain development; Fetal alcohol spectrum disorders; Neuroinflammation; Peroxisome proliferator-activated receptors; Therapy

Introduction

Fetal alcohol spectrum disorders (FASD) result from ethanol exposure during pregnancy, and are the leading cause of mental retardation [1]. An alarming 2-5% of children born in the United States have FASD [2]. Due to the complex, orchestrated processes underway in the developing CNS, it is not surprising that individuals with FASD present a variety of CNS sequelae that often persist throughout life. Neuropathologies associated with FASD are widespread and cause an array of mild to severe cognitive and behavioral impairments [3,4]. In spite of the devastating personal and societal impact of FASD, there remains no cure for these disorders.

Commentary

Animal models of FASD have been developed that exhibit many of the same neuropathology and associated behavioral deficits observed in human FASD. The consequences of ethanol exposure during CNS development in animal models reveals brain malformation, neurodegeneration, altered neural circuitry, impaired learning and memory, and more, recapitulating the human condition [5]. These FASD models are critical to defining the mechanisms that regulate ethanol-induced pathology in the developing CNS, which is critical to establishing effective therapies for these disorders. We and others have demonstrated that ethanol induces significant neuroinflammation in the developing CNS using neonatal rodents to model maternal alcohol consumption during the third trimester of pregnancy [5]. We discovered that ethanol increased the activation of microglia [6], which are endogenous immune cells in the CNS. Ethanol-induced neuroinflammation was associated with loss of cerebellar neurons in these studies suggesting that neuroinflammation may contribute to neurodegeneration. Recently, in studies which are the subject of this commentary, we demonstrated that ethanol also induced the production of pro-inflammatory cytokines including IL-1β and TNF-α and chemokine CCL2 not only in the developing cerebellum, but also in the hippocampus and cerebral cortex [7]. This suggests that ethanol can induce more global neuroinflammation. Studies by Tiwari et al. [8] also revealed neonatal exposure to ethanol resulted in increased expression of the cytokines IL-1β and TNF-α, and the transcription factor NF-κB in the cerebral cortex and hippocampus. Recent studies by Topper et al. [9] support these findings with microglial activation and increased IL-1β and TNF-α in the cerebellum and hippocampus at various intervals during and after neonatal alcohol exposure. In addition, recent studies by Boschen et al. [10] demonstrated microglial activation, although analysis of cytokine levels was confounded by disparity in control groups. The observation that ethanol commonly induces IL-1β in these studies suggests a role for inflammasomes because inflammasomes play a critical role in IL-1β processing [11]. Thus, our studies and those of others reveal that ethanol induction of neuroinflammation is multifaceted including microglial activation and expression of pro-inflammatory neuroimmune molecules.

Multiple studies in mouse models provide evidence that even transient neuroinflammation during critical stages of development has long-term, detrimental impact on behavior in adults [12-14]. In addition, transient reduction of microglial cell populations resulted in aberrant development. For example, genetic deletion of CX3CR1, which is expressed by microglia in the CNS, resulted in transient loss of microglia and aberrant synaptic pruning, leading to behavioral deficits in adulthood [15]. These mice also demonstrated impaired synaptic plasticity in the hippocampus and cognition as adults [16]. Our studies [7] that are the focus of this commentary identified microglial activation and neuroinflammatory molecules in brain regions that are high-profile targets of pathogenesis in FASD. Ethanol

induction of neuroinflammation in the cerebral cortex and hippocampus is particularly meaningful given the wide spectrum of cognitive and behavioral disabilities associated with FASD. The effects of alcohol exposure during fetal development produce lasting consequences, including learning and memory deficits, mood disturbances, and increased risk of substance abuse in adulthood [17-21]. Imaging studies in individuals with FASD demonstrate changes in structure and neural circuitry in these regions that correlate with the severity of cognitive dysfunction [19-21]. Animal models of FASD also document neurodegeneration, disrupted neural plasticity, learning and memory deficits, altered activity levels, and anxiety [5]. In addition, the presence of neuroinflammation in the cerebellum is meaningful in context of the often overlooked, but significant, motor function disabilities and cerebellar-linked cognitive deficits in many individuals with FASD [17,18,20-23]. Based on these facts, we argue that the transient expression of neuroinflammation, including microglial activation and pro-inflammatory cytokine expression, induced by fetal alcohol exposure may be a unifying mechanism in multiple brain regions that leads to neurodegeneration, disruption of neural plasticity and neural circuitry, and cognitive and other behavioral disabilities.

Ethanol induces neuroinflammation in multiple brain regions in FASD models [7,8] and these brain regions are associated with ethanol-induced behavioral deficits. This suggested that anti-inflammatory agents may be effective in suppressing ethanol-induced neuroinflammation and could be effective in blocking ethanol-induced neuropathologies. We and others had previously demonstrated that peroxisome proliferator-activated receptor (PPAR)-γ agonists suppress neuroinflammation in animals models of neurodegenerative disorders including multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis, and stroke [24-27]. In the studies which are the subject of this commentary, we demonstrated that the PPAR-γ agonist pioglitazone suppressed microglial activation and cytokine/chemokine production in multiple brain regions including the cerebral cortex, hippocampus, and cerebellum [7]. This suggests that PPAR-γ agonists may be effective in blocking ethanol-induced cognitive and motor deficits common to FASD. Although the PPAR-γ agonist pioglitazone is commonly used in the treatment of type II diabetes, we are just beginning to investigate its potential for prevention and treatment of FASD. The PPAR-γ agonist docosahexaenoic acid (DHA) has strong potential as a therapeutic for FASD. DHA is believed to be safe to the developing fetus, and in fact has been demonstrated to increase problem solving skills in infants whose mothers received DHA as a supplement during pregnancy or who were provided infant formula containing DHA [28,29]. Studies indicating that DHA blocked neuroinflammation and neuron loss in response to ethanol *in vivo* in rat hippocampal-entorhinocortical cultures [30] and blocked somatosensory system-dependent behavioral deficits *in vivo* in rats treated prenatally with ethanol [31] further support the potential of DHA for the treatment of FASD. In adults, alcohol consumption increases neuroinflammation and, in turn, neuroinflammation increases alcohol consumption as well as development of alcohol use disorders. In this context, it is interesting PPAR-γ agonists have been demonstrated to suppress alcohol drinking behavior in rodents [32,33]. PPAR-γ agonists may reduce alcohol consumption by suppressing neuroinflammation. Thus, PPAR-γ agonists may be effective in treating adult alcohol use disorders as well as FASD.

The studies outlined above suggest that anti-inflammatory agents including PPAR-γ agonists may be effective in suppressing ethanol-induced neuroinflammation and may be effective in the treatment of behavioral deficits associated with FASD. Additional studies are needed to determine the precise mechanisms by which ethanol elicits neuroinflammation in FASD in order to developed targeted therapies for these disorders. Elegant studies by the laboratories of Crews, Guerri, and Szabo indicate that TLR4, HMGB1, and inflammasome molecules play critical roles in ethanol-induced neuroinflammation in adult rodent models [34-36]. Ethanol also induces epigenetic modification in the CNS [37] and should be considered as an additional mechanism through which ethanol may modulate neuroinflammation. Determining the inflammatory molecules and other immune signaling pathways that control ethanol-induced neuroinflammation in the developing CNS is critical to defining novel therapies for FASD.

Acknowledgements

This work was supported by NIH NIA grants AA018834, AA023723, AA024695, and NIGMS IDeA program award P30 GM110702.

References

1. Abel EL, Sokol RJ (1986) Fetal alcohol syndrome is now leading cause of mental retardation. Lancet 2: 1222.
2. May PA, Baete A, Russo J, Elliott AJ, Blankenship J, et al. (2014) Prevalence and characteristics of fetal alcohol spectrum disorders. Pediatrics 134: 855-866.
3. Lebel C, Roussotte F, Sowell ER (2011) Imaging the impact of prenatal alcohol exposure on the structure of the developing human brain. Neuropsychol Rev 21: 102-118.
4. Mattson SN, Roesch SC, Glass L, Deweese BN, Coles CD, et al. (2013) Further development of a neurobehavioral profile of fetal alcohol spectrum disorders. Alcohol Clin Exp Res 37: 517-528.
5. Drew PD, Kane CJ (2014) Fetal alcohol spectrum disorders and neuroimmune changes. Int Rev Neurobiol 118: 41-80.
6. Kane CJM, Phelan KD, Han L, Smith RR, Xie J, et al. (2011) Protection of neurons and microglia against ethanol in a mouse model of fetal alcohol spectrum disorders by peroxisome proliferator-activated receptor-gamma agonists. Brain Behav Immun 25 Suppl 1: S137-145.
7. Drew PD, Johnson JW, Douglas JC, Phelan KD, Kane CJ (2015) Pioglitazone blocks ethanol induction of microglial activation and immune responses in the hippocampus, cerebellum, and cerebral cortex in a mouse model of fetal alcohol spectrum disorders. Alcohol Clin Exp Res 39: 445-454.
8. Tiwari V, Chopra K (2011) Resveratrol prevents alcohol-induced cognitive deficits and brain damage by blocking inflammatory signaling and cell death cascade in neonatal rat brain. J Neurochem 117: 678-690.
9. Topper LA, Baculis BC, Valenzuela CF (2015) Exposure of neonatal rats to alcohol has differential effects on neuroinflammation and neuronal survival in the cerebellum and hippocampus. J Neuroinflammation 12: 160.
10. Boschen KE, Ruggiero MJ, Klintsova AY (2016) Neonatal binge alcohol exposure increases microglial activation in the developing rat hippocampus. Neuroscience 324: 355-366.
11. Guo H, Callaway JB, Ting JP (2015) Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med 21: 677-687.
12. Bilbo SD, Smith SH, Schwarz JM (2012) A lifespan approach to neuroinflammatory and cognitive disorders: a critical role for glia. J Neuroimmune Pharmacol 7: 24-41.
13. Schwarz JM, Bilbo SD (2012) The immune system and the developing brain. In: McCarthy MM (ed) Colloquium series on the developing brain. Morgan & Claypool Life Sciences. San Rafael, California pp: 1-118.

14. Green HF, Nolan YM (2014) Inflammation and the developing brain: consequences for hippocampal neurogenesis and behavior. Neurosci Biobehav Rev 40: 20-34.
15. Zhan Y, Paolicelli RC, Sforazzini F, Weinhard L, Bolasco G, et al. (2014) Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. Nat Neurosci 17: 400-406.
16. Rogers JT, Morganti JM, Bachstetter AD, Hudson CE, Peters MM, et al. (2011) CX3CR1 deficiency leads to impairment of hippocampal cognitive function and synaptic plasticity. J Neurosci 31: 16241-16250.
17. Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, et al. (2004) Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. J Dev Behav Pediatr 25: 228-238.
18. Mattson SN, Crocker N, Nguyen TT (2011) Fetal alcohol spectrum disorders: Neuropsychological and behavioral features. Neuropsychol Rev 21: 81-101.
19. Joseph J, Warton C, Jacobson SW, Jacobson JL, Molteno CD, et al. (2014) Three-dimensional surface deformation-based shape analysis of hippocampus and caudate nucleus in children with fetal alcohol spectrum disorders. Hum Brain Mapp 35: 659-672.
20. Glass L, Ware AL, Mattson SN (2014) Neurobehavioral, neurologic, and neuroimaging characteristics of fetal alcohol spectrum disorders. Handb Clin Neurol 125: 435-462.
21. Norman AL, Crocker N, Mattson SN, Riley EP (2009) Neuroimaging and fetal alcohol spectrum disorders. Dev Disabil Res Rev 15: 209-217.
22. Diwadkar VA, Meintjes EM, Goradia D, Dodge NC, Warton C, et al. (2013) Differences in cortico-striatal-cerebellar activation during working memory in syndromal and nonsyndromal children with prenatal alcohol exposure. Hum Brain Mapp 34: 1931-1945.
23. Connor PD, Sampson PD, Streissguth AP, Bookstein FL, Barr HM (2006) Effects of prenatal alcohol exposure on fine motor coordination and balance: A study of two adult samples. Neuropsychologia 44: 744-751.
24. Diab A, Deng C, Smith JD, Hussain RZ, Phanavanh B, et al. (2002) Peroxisome proliferator-activated receptor-γ agonist 15-deoxy-delta(12,14)-prostaglandin J(2) ameliorates experimental autoimmune encephalomyelitis. J Immunol 168: 2508-2515.
25. Heneka MT, Landreth GE, Feinstein DL (2001) Role for peroxisome proliferator-activated receptor-gamma in Alzheimer's disease. Ann Neurol 49: 276.
26. Kiaei M, Kipiani K, Chen J, Calingasan NY, Beal MF (2005) Peroxisome proliferator-activated receptor-gamma agonist extends survival in transgenic mouse model of amyotrophic lateral sclerosis. Exp Neurol 191: 331-336.
27. Tureyen K, Kapadia R, Bowen KK, Satriotomo I, Liang J, et al. (2007) Peroxisome proliferator-activated receptor-γ agonists induce neuroprotection following transient focal ischemia in normotensive, normoglycemic as well as hypertensive and type-2 diabetic rodents. J Neurochem 101: 41-56.
28. Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA (2003) Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. Pediatrics 111: e39-44.
29. Willatts P, Forsyth JS, DiModugno MK, Varma S, Colvin M (1998) Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. Lancet 352: 688-691.
30. Tajuddin N, Moon KH, Marshall SA, Nixon K, Neafsey EJ, et al. (2014) Neuroinflammation and neurodegeneration in adult rat brain from binge ethanol exposure: abrogation by docosahexaenoic acid. PLoS One 9: e101223.
31. Wellmann KA, George F, Brnouti F, Mooney SM (2015) Docosahexaenoic acid partially ameliorates deficits in social behavior and ultrasonic vocalizations caused by prenatal ethanol exposure. Behav Brain Res 286: 201-211.
32. Blednov YA, Benavidez JM, Black M, Ferguson LB, Schoenhard GL, et al. (2015) Peroxisome proliferator-activated receptors α and γ are linked with alcohol consumption in mice and withdrawal and dependence in humans. Alcohol Clin Exp Res 39: 136-145.
33. Stopponi S, Somaini L, Cippitelli A, Cannella N, Braconi S, et al. (2011) Activation of nuclear PPARγ receptors by the antidiabetic agent pioglitazone suppresses alcohol drinking and relapse to alcohol seeking. Biol Psychiatry 69: 642-649.
34. Alfonso-Loeches S, Pascual-Lucas M, Blanco AM, Sanchez-Vera I, Guerri C (2010) Pivotal role of TLR4 receptors in alcohol-induced neuroinflammation and brain damage. J Neurosci 30: 8285-8295.
35. Lippai D, Bala S, Petrasek J, Csak T, Levin I, et al. (2013) Alcohol-induced IL-1β in the brain is mediated by NLRP3/ASC inflammasome activation that amplifies neuroinflammation. J Leukoc Biol 94: 171-182.
36. Vetreno RP, Crews FT (2012) Adolescent binge drinking increases expression of the danger signal receptor agonist HMGB1 and toll-like receptors in the adult prefrontal cortex. Neuroscience 226: 475-488.
37. Jangra A, Sriram CS, Pandey S, Choubey P, Rajput P, et al. (2016) Epigenetic Modifications, Alcoholic Brain and Potential Drug Targets. Ann Neurosci 23: 246-260.

This article was originally published in a special issue, entitled: **"Neuroinflammatory Diseases",** Edited by Dr. Michael C. Levin, University of Tennessee Health Science Center, USA